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Review

Does endoscopic treatment for early oesophageal cancers give equivalent oncological outcomes as compared with oesophagectomy? Best evidence topic (BET)

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ABSTRACT

A best evidence topic was written according to a structured protocol. The question addressed was whether endoscopic mucosal resection (EMR) for early oesophageal cancer gives equivalent oncological outcomes as compared to oesophagectomy. A total of 340 papers were found using the reported searches of which 7 represented the best evidence to answer the clinical question. The authors, date, journal, study type, population, main outcome measures and results are tabulated. Oesophagectomy with lymph node dissection for early oesophageal cancer is the standard to which every other treatment modality is compared to. However, the associated mortality and morbidity rates highlight the need for the development of effective, less invasive procedures. The evidence from the present review supports the use of EMR in this context as a first line treatment in T1a (mucosal) oesophageal cancer. The trade-off is a higher recurrence rate which can be dealt with successfully using a tight follow-up schedule and retreatment. The higher rates of lymph node involvement in T1b (submucosal) cancers preclude the use of endoscopic treatment in this setting except for patients unfit for surgery.

1. Introduction

A best evidence topic was constructed according to a structured protocol. This protocol is fully described in the International Journal of Surgery.[1]

2. Clinical scenario

A colleague with Barrett's oesophagus under surveillance meets you during lunch and states that recent biopsies revealed intramucosal cancer and a subsequent EUS did not demonstrate submucosal invasion. He then asks for your opinion on whether an endoscopic treatment with EMR would be sufficient or surgical treatment would be more appropriate. You resolve to assess the literature yourself.

3. Three-part question

In [patients with early oesophageal cancer] do [EMR] and [oesophagectomy] give equivalent [oncological outcomes]?

4. Search strategy

Search strategy using Medline from 1948 to December 2011 using the PubMed interface: 'Endoscopic therapy' AND 'Oesophagectomy' AND 'Early oesophageal cancer'. Reference lists of key articles were also searched for references.

5. Search outcome

A total of 340 papers were found using the above search. After reviewing the abstracts 24 papers were selected to be fully appraised in view of relevance and methods used. Based on design,

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number of patients and origin (high volume/specialised centres and national registries) 7 papers written in English were identified that provided the best evidence to answer the question. These are presented in Table 1.

6. Discussion

There is no randomised controlled trial to this date addressing the issue of endoscopic mucosal resection (EMR) vs oesophagectomy for early oesophageal cancer. Moreover, the observed heterogeneity among the relevant studies makes their interpretation difficult.

Identification of low-risk oesophageal cancers gives these patients the best chance of being treated successfully by complete local excision, thus leading to optimal preservation of organ function and avoiding potential peri-operative complications. The presence of lymphatics in the deep mucosa renders oesophagus unique among viscous hollow organs of the gastrointestinal tract. In this context, studies like the one by Cen et al.[2] that retrospectively studied the lymph node metastasis (LNM) and lymphovascular invasion status (LVI) in the largest group of T1 oesophageal cancers, aid significantly in decision making. In this study, it was demonstrated that LNM rate is 4% in the T1a group (invasion up to muscularis mucosa) as compared to 26% in T1b patients (invasion of the submucosa) with subsequent implications on recurrence rate and overall survival. These findings are in accordance with the existing literature on the subject.[3,4,5] It has also been proved that previous EMR does not preclude subsequent oesophagectomy.[6] Hence, if pathology demonstrates a higher stage than initially perceived a completion oesophagectomy can follow. As a result, contemporary clinical practice endorses oesophagectomy with radical lymph node clearance for T1b tumours, whilst both oesophagectomy and EMR may be contemplated for T1a tumours. This is also incorporated in oesophageal cancer treatment guidelines such as the NCCN guidelines.[7]

Pech et al.[8] retrospectively reviewed 114 patients with T1a oesophageal adenocarcinoma on the background of Barret's oesophagus that underwent either oesophagectomy ($n = 38$) or EMR plus argon-plasma-coagulation (APC, $n = 76$), in two high volume centres in Germany between 1996 and 2009. Median follow up was 3.7 and 4.1 years respectively, with a strict follow-up program implemented after endoscopic treatment. Both modalities proved equally effective and no tumour related mortality was observed in either group. Long-term complete remission [CR] was 100% for surgical and 98.7% for endoscopic treatment (one patient died of other causes before CR was achieved). Five year overall survival was 89% for EMR and 93% for surgery ($p = 0.91$). Surgery was associated with higher morbidity (major complications 32%) and procedure related mortality risk (2.6% at 90 days). On the other hand, EMR plus APC was safer (0% major complications) with the disadvantage of higher relapse rate (6.6%), requiring repeat endoscopic treatment which was feasible and successful in all cases. No patient required oesophagectomy after initial EMR.

Prasad et al.[9] compared the long-term outcomes of 178 patients treated either endoscopically ($n = 132$, EMR or EMR plus photodynamic therapy [PDT]) or surgically ($n = 46$, transthoracic or transhiatal route) for T1a oesophageal adenocarcinoma with a mean follow up period of 43 and 64 months respectively. Five year overall survival was 83% in the EMR and 95% in the surgery group ($p < 0.001$) and cumulative mortality was 17% and 20% respectively ($p = 0.75$). A higher recurrence rate was detected in the EMR group (12%) requiring repeat endoscopic treatment. Complication rate was higher with oesophagectomy (34% vs 13% for EMR). The study is limited by the smaller number of patients and longer Barrett's oesophagus segment in the oesophagectomy arm. On the other hand, patients treated endoscopically were older (mean age of 71.2 vs 67.7, $p = 0.006$) with more comorbidities.

Das et al.[10] retrospectively reviewed 742 patients registered between 1998 and 2003 with the diagnosis of Tis (high grade dysplasia, 17.7%) or T1N0M0 (mucosal-submucosal, 82.3%) oesophageal cancer in the Surveillance Epidemiology and End Results database (SEER) of the National Cancer Institute in the USA. The histologic type was non-squamous in 83.7% of patients (mainly adenocarcinoma) and squamous in 16.3%. The patients received either surgical (86.7%) or endoscopic therapy (13.3%). In the latter group 65.7% underwent EMR, 14.1% EMR plus ablation [thermal or photodynamic therapy (PDT)] and 16.2% solely ablation. Endoscopic therapy was not specified in 4 patients. The conclusion was that EMR and surgery are equally effective. Median oesophageal cancer-free survival was 59 months in the surgical resection group versus 56 months in the endoscopic therapy group (primary outcome, $p = 0.41$). Oesophageal cancer-specific mortality was similar for endoscopic and surgical treatment with a relative hazard [RH] of 0.89 (95% confidence interval [CI] 0.51–1.56, $P = 0.68$). Limitations include the lower percentage of patients and inhomogeneous treatment in the endoscopic therapy group, and the lack of data on provider- and hospital-level. With regard to the primary outcome all histologic types were grouped together and no separate analysis was performed. The same applies to T1a/T1b cancers. The exclusion of 20 patients that were not treated with EMR did not affect the overall conclusion.

Schembre et al.[11] conducted a retrospective review of a single institution's experience in endoscopic and surgical treatment with curative intent of patients with Barrett's oesophagus and high grade dysplasia (HGD, $n = 63$) or intramucosal adenocarcinoma (IMC, $n = 30$). A total of 62 procedures were completed endoscopically (18 EMR, 22 EMR plus PDT, 20 PDT and 2 APC) and 32 surgically (4 transhiatal, 10 Ivor-Lewis, 18 left thoracoabdominal). The median follow-up was 20 months for endoscopic treatment and 48 months for oesophagectomy. Overall 4-year adjusted survival rate was 89% for endotherapy and 93% for surgery ($p = 0.49$) with no deaths attributed to oesophageal cancer for either group. Eight patients with HGD in the endotherapy group underwent further endoscopic therapy for residual disease. Cancer developed in 6% of patients with an initial diagnosis of HGD that were treated endoscopically (1 IMC that underwent repeat endotherapy, 1 IMC that opted for surgery and 2 invasive cancers that received chemoradiation). One patient in the surgical group with persistent HGD proximal to a high anastomosis was treated successfully endoscopically. For endoscopic treatment, procedure related mortality was 2% (1 patient died of sepsis from diverticulitis 11 days after treatment), major complications were 8% and minor complications 32%. The respective percentages for oesophagectomy were 0%, 13% and 66%. Authors conclude that endoscopic therapy is equally effective. The study is limited by the inhomogeneous treatment modalities, higher patient age (70 vs 64 years) and relatively short follow-up in the endotherapy arm. Also, by the small numbers and the retrospective design.

Pacifico et al.[12] retrospectively analysed the results of either EMR plus photodynamic therapy (PDT) or oesophagectomy in 88 patients with early adenocarcinoma (T1a/T1b) on a background of Barrett's oesophagus. Twenty-four received endoscopic therapy while the rest underwent surgery. Mean follow-up time was 19 months in the oesophagectomy and 12 months in the EMR/PDT group. Treatment-related complication rate was higher in the oesophagectomy group (31% vs 4%) and 1 procedure related death was observed (vs 0). In the EMR/PDT group persistent adenocarcinoma was found in 4 patients (17%) on the first follow-up examination (1 underwent oesophagectomy, 1 received chemoradiation as a high-risk surgical candidate and two died of causes unrelated to cancer progression or to

Table 1
Best evidence papers.

Author, date and country, study type (level of evidence)	Patient group	Outcomes	Key results	Comment
Pech et al. 2011[8] Ann Surg. Germany Retrospective cohort study (Level 3 evidence)	A total of 114 patients with mucosal BC who were treated either surgically or endoscopically between 1996 and 2009 in two high-volume centers. Thirty-eight patients received transthoracic esophageal resection with 2-field lymphadenectomy (median 29 lymph nodes removed; all pN0). Seventy-six patients treated with EMR followed by argon-plasma-coagulation of the remaining non-dysplastic Barrett's oesophagus. Patients were matched according to age, gender, infiltration depth (pT1m1-3), differentiation grade (G1/2 vs. 3) and follow-up period. The median follow-up periods were 4.1 years in the ER group and 3.7 years in the surgical group	Complete remission (CR) Major complications Ninety day mortality Overall recurrence rate Disease free follow-up (5 years) Overall survival (5 years) Tumor related mortality	*EMR vs. Oesophagectomy* 98.7% (1 patient died of other causes before achieving CR) vs 100% 0% vs. 32% ($p < 0.001$) 0% vs. 2.6% ($p = 0.333$) 6.6% (1 local, 4 metachronous with successful repeat endoscopic treatment in all patients) vs. 0% ($p = 0.17$) 91% vs 100% ($p = 0.19$) 89% vs 93% ($p = 0.91$) 0% in both groups.	No LNM noted in both groups. For patients with mucosal BC, both surgery and EMR are effective treatment modalities. Surgery is associated with a higher morbidity rate and shows a risk for procedure-related mortality. The recurrence rate is higher in patients treated with EMR, hence thorough follow-up is mandatory.
Prasad et al. 2009[9] Gastroenterology USA Retrospective cohort study (Level 3 evidence)	Retrospective analysis of 178 patients treated for mucosal (T1a) oesophageal adenocarcinoma between 1998 and 2007. Patients were divided into an endoscopically treated group ($n = 132$, 111 male, mean age 71.2 years) and a surgically treated group ($n = 46$, 43 male, mean age 67.7 years). The mean follow-up period was 64 months (standard error of the mean 4.8 months) in the oesophagectomy group and 43 months (standard error of the mean 2.8 months) in the EMR group. Median age-adjusted Charlson Comorbidity Index, (IQR) was 4 (0–5) in the EMR and 0 (0–4) in the surgery arm ($p < 0.001$)	Complication rate Cumulative mortality Cancer free survival (5 years) Overall survival (5 years) Recurrence	*EMR vs. Oesophagectomy* 13% vs 34% 17% vs. 20% ($p = 0.75$) 80% vs 97% ($p = 0.33$) 83% vs 95% ($p < 0.001$) 16/132 (all successfully retreated without an impact on survival) vs 1/46	Authors conclude that outcome is comparable between EMR and esophagectomy. Limitations: Retrospective analysis. Smaller number of patients with longer Barrett's oesophagus segment in the surgery arm. Older patients with more comorbidities in the EMR arm.
Cen et al. 2008[2] Cancer USA Retrospective cohort study (Level 3 evidence)	Ninety nine patients with T1,N0 or T1,N1 adenocarcinoma of the oesophagus or the GOJ who underwent primary oesophagectomy at the University of Texas M. D. Anderson Cancer Center between November 1988 and November 2005. Preoperative assessment comprised upper GI endoscopy with biopsies, EUS, CT and in 32 patients (32.3%) also a PET scan. All 99 patients underwent resection with lymph node dissection for curative intent. No patient received adjuvant chemotherapy or chemoradiation after surgery The following data were obtained: size, depth, location of the cancer, LVI status, degree of differentiation, presence of Barrett's mucosa, margin status, and the presence or absence of LNM The time to relapse and location of relapse (local and distant), the date of death, and the cause of death were ascertained. Mean follow up 60 months.	LNM Overall survival (OS) and survival prognosis Recurrence-free survival (5 years)	*T1a vs. T1b* 4% vs 23% 88% (all non-cancer related deaths) vs 62% 5 year OS ($p = 0.001$) [T1a vs T1b without LVI is 90% vs 77%, $p = 0.078$. T1b without LVI vs T1b with LVI is 77% vs 27% $p = 0.006$] The multivariate analysis demonstrated that LNM ($P = 0.03$) and age >65 years ($P = 0.04$) were independent factors that were predictive of a poor OS. The presence of LVI was of borderline significant as an independent factor that was predictive of poor OS ($P = 0.05$) 100% vs 74% (T1b without LVI, $p = 0.006$), 35% (T1b with LVI, $p < 0.0001$). Distant metastasis in 96% of patients with recurrence	Low risk for LNM in T1a as compared to T1b cancers. This endorses the concept of less invasive procedures such as EMR being used as first line treatment in T1a cancers.

(*continued on next page*)

Table 1 (*continued*)

Author, date and country, study type (level of evidence)	Patient group	Outcomes	Key results	Comment
Das et al. 2008[10] Am J Gastroenterol. USA Retrospective cohort study (Level 3 evidence)	A total of 742 patients registered between 1998 and 2003 in the Surveillance Epidemiology and End Results database (SEER) of the National Cancer Institute, with the diagnosis of Tis (high grade dysplasia) or T1N0M0 nonsquamous and squamous cell-type esophageal cancer Ninety nine (13.3%) patients underwent endoscopic treatment (group A) and the remainder was managed by surgical resection (group B). Endoscopic treatment comprised EMR (65.7%), EMR plus ablative therapy (14.1%) and ablative therapy alone (16.2%). Data on demographic features, tumour characteristics, types of treatment received (endoscopic vs surgical resection), and cancer-specific mortality were analyzed.	Cancer specific mortality Median cancer-free survival Predictors of survival	*Endoscopic therapy vs. Oesophagectomy* Cox proportional hazards model demonstrates a relative hazard [RH] of 0.89 (95% confidence interval [CI] 0.51–1.56, $P = 0.68$) 56 vs 59 months, $p = 0.41$. Significant predictors of survival were age at diagnosis (RH 1.06, 95% CI 1.03–1.08, $P < 0.001$) and absence of exposure to radiation therapy (RH 0.32, 95% CI 0.21–0.48, $P < 0.001$).	Equivalent long term survival between endoscopic therapy and surgery in early oesophageal cancer. Cumulative experience from multiple institutions, not only highly-specialised, high-volume centres. First population-based data supporting the effectiveness of endoscopic therapy for managing these patients. Radiation therapy detrimental to overall survival. Limitations: Small percentage of endoscopically treated patients, with inhomogeneous treatment modalities.
Schembre et al. 2008[11] Gastrointest Endosc USA Retrospective cohort study (Level 3 evidence)	A retrospective study of 94 patients with Barrett's oesophagus and dysplasia or intramucosal cancer who received either endoscopic or surgical therapy between 1998 and 2005 was performed. Sixty-two patients with a median age of 70 years underwent endoscopic therapy (2 APC alone, 18 EMR + APC, 20 PDT + APC, and 22 EMR + PDT + APC). Seventy three percent were male. Thirty two patients underwent oesophagectomy (93% male with a median age of 64 years). Average ASA level was 2.6 in the endotherapy and 2.5 in the surgery group. Median follow-up of 20 months for endotherapy and 48 months for surgery.	Oesophageal cancer-related mortality Thirty day mortality Cancer recurrence rate Major/ Minor complications Median cost	*Endoscopic therapy vs. Oesophagectomy* 0% in both groups 1 (2%) vs 0% ($p = 0.49$) 6% vs 0% ($p < 0.05$) 8% / 31% vs 13% / 63% ($p = 0.5$ / $p < 0.001$) $40,079 vs $66,060 ($p < 0.001$)	Modalities equally effective. Higher morbidity and cost for surgery. Higher risk of recurrence with endoscopic therapy mandating careful follow up. Limitations: Retrospective analysis. Small numbers. Relatively short follow up with higher patient age and inhomogeneous treatment modalities in the endoscopic therapy group.
Pacifico et al. 2003[12] Clin Gastroenterol Hepatol USA Retrospective cohort study (Level 3 evidence)	Retrospective study (1996–2001) of 88 patients with early stage BC undergoing either EMR plus an ablative procedure (PDT, $n = 24$, 21 men, mean age 68 years) or oesophagectomy ($n = 64$, 58 male, mean age 67 years). Follow-up of 12 ± 2 and 19 ± 3 months respectively. Pulmonary comorbidities were significantly higher in the EMR/PDT group (42% vs 19%, $p = 0.03$). Patient demographics, tumor staging, procedure-related morbidity and mortality, persistence or recurrence of cancer, and cancer-related deaths after therapy were studied.	Procedure-related complications Procedure-related deaths Failure to respond to therapy Cancer free at the end of follow-up	*EMR/PDT vs Oesophagectomy* 31 vs 4 ($p < 0.01$) 0 vs 1 4 (2 underwent alternative therapies and rendered free of disease, 2 died of unrelated causes) vs 0 83% (20/24) vs 100%	Endoscopic therapy appears to constitute a viable option for the treatment of early Barrett's adenocarcinoma. Limitations: Small number of patients in the endoscopic therapy group. Retrospective study. Short follow-up. Higher pulmonary comorbidities in the EMR/PDT group. Lack of discrimination between T1a and T1b stage.
Fujita et al. 2001[13] World J Surg Japan Retrospective cohort study (Level 3 evidence)	A total of 150 patients diagnosed with T1a ($n = 72$) or T1b ($n = 78$) oesophageal cancer from 1981 to 1997 were evaluated (17 women and 133 men, mean age of 63 years). Mortality and morbidity rates, survival rate, and recurrence rate were retrospectively compared for (1) 35 patients who underwent EMR and 37 patients who underwent oesophagectomy for a mucosal oesophageal cancer and (2) 45 patients who underwent extended radical oesophagectomy and 33 patients who underwent less radical oesophagectomy for a submucosal oesophageal cancer. Follow-up of 32 months in average (4–68) for the EMR and 62 months (1–153) for the oesophagectomy group.	LNM Survival (5-year) Hospital Mortality Morbidity Recurrence	*T1a vs T1b* 1% vs 38% *EMR vs Oesophagectomy (T1a)* 61% vs 71% (p = NS) No difference in disease specific survival 0% vs 14% ($p = 0.017$) 7% vs 69% ($p < 0.001$) 0% vs 0%	No difference in survival and recurrence rates in T1a oesophageal cancers treated with either EMR or oesophagectomy. Significantly lower morbidity and mortality with EMR. Authors conclude that EMR should be a mainstay treatment for T1a cancers. Substantially lower LNM rate in the T1a group. Limitations: retrospective analysis.

APC = Argon-Plasma-coagulation; BC = Barrett's Cancer (adenocarcinoma); CI = confidence interval; EMR = Endoscopic Mucosal Resection; GI = Gastrointestinal; GOJ = Gastrooesophageal junction; OR = odds-ratio; PET = positron emission tomography; PDT = photodynamic therapy; LNM = lymph node metastasis; LVI = lymphovascular invasion.

treatment). No other patient in both groups had cancer detected during follow-up. The authors conclude that endoscopic therapy is a viable, less morbid alternative to surgery. Weaknesses of the study comprise the retrospective design, the relatively short follow-up and the smaller number of patients in the EMR/PDT group. Moreover, there was a higher proportion of pulmonary comorbidities (42% vs 19%, $p = 0.03$) in this group. No discrimination was made between T1a and T1b stage.

Fujita et al.[13] retrospectively reviewed 150 patients with T1a ($n = 72$) or T1b ($n = 78$) squamous cell oesophageal cancer. The former group received either EMR or oesophagectomy (transthoracic route with lymphadenectomy in 23 and transhiatal route without lymphadenectomy in 12 patients). The latter underwent extended radical or less radical oesophagectomy. The average follow-up period was 32 months (range 4–68) for EMR and 62 months (range 1–153) for surgery. There was no significant difference in background factors between the oesophagectomy and the EMR group. Fifteen patients were cancer-positive at the lateral margin after EMR, but repeated EMR, endoscopic laser vaporization, or adjuvant radiotherapy were successful, so no patient died of recurrence. Adjuvant radiotherapy was administered to 4 of these patients because the presence of oesophageal varices or oesophageal stricture precluded repeat EMR. There was no significant difference in the overall survival curves. The overall 5-year survival rate after EMR was 61%, and the 5- and 10-year survival rates after oesophagectomy were 71% and 42%. Survival of patients with mucosal oesophageal cancer was strongly influenced by the postoperative complications and the presence of synchronous double primary cancers (36% of cases) but not by the treatment modality (EMR versus esophagectomy). There was no difference between the two modalities in disease specific survival since no patient died of recurrence in both groups. In T1a cancers, hospital mortality and morbidity were 0% and 7% after EMR and 14% and 69% after oesophagectomy. Of note the LNM/LN recurrence rate of 1% for T1a tumours compared to 38% for T1b. The authors, in view of the equivalent outcomes and safety profile, conclude that EMR and extended radical oesophagectomy is the mainstay of treatment for T1a and T1b tumours respectively. The study is limited by the retrospective design.

Three more facts should be mentioned, that provide reason for additional contemplation. Firstly, the Eguchi et al.[14] study which suggests a higher (18%) lymph node involvement rate in m3 (muscularis mucosa) squamous-cell oesophageal cancer, rendering these patients unsuitable for endoscopic treatment. Secondly, the Wiesbaden group experience which has shown that patients with sm1 (upper third of submucosa) oesophageal adenocarcinoma may be considered for endoscopic resection alone if the cancers are low grade and do not demonstrate lymphovascular infiltration.[15] And lastly, the fact that the successful results with EMR come from high volume, highly specialized centers which commands for caution when applying them in clinical decision making.

7. Clinical bottom line

The lack of high level evidence in the literature highlights the need for further studies. However, given the ethical implications, the long follow-up time and the standardization of treatment modalities required, such a study seems unlikely to occur in the foreseeable future. In addition, performance of minimally invasive oesophagectomy may shift the tables in terms of morbidity and mortality but that remains to be proved.

Based on the available evidence, endoscopic mucosal resection alone or combined with other endoscopic techniques represents a viable and less invasive therapeutic option for early oesophageal cancer. It seems to offer equivalent oncological outcomes compared to oesophagectomy for T1a cancers, with significantly decreased morbidity and mortality. Endoscopic treatment appears to be associated with higher recurrence rates, but this may be successfully managed in the majority of the cases with close follow-up and repeat endoscopic treatment. On the other hand, surgery is considered the best available treatment for T1b cancers due to the higher incidence of lymph node involvement. In patients with T1a oesophageal cancer an extensive discussion with the patient is advocated, as it all comes down to choosing between a safer procedure entailing life-long thorough follow-up with possible reinterventions, or risking significantly higher morbidity and mortality for a long lasting positive treatment outcome.

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Conflicts of interest

There are no conflicts of interest.

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